Magneto Resistive-Based Biosensors and Biochips

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***ABSTRACT:** Protein biochips are at the heart of many medical and bioanalytical processes applications, please. Increased interest was focused on surface activation and associated functionalization methods for the activation of these biomolecules. Over the past five years, magneto electronics has emerged as a promising new platform technology for biosensor and biochip production. The techniques are based on the identification of the magnetic fringe field of a magnetically labelled biomolecule interacting with a complementary biomolecule attached to a magnetic-field sensor. Magneto resistive-based devices, easily used as read heads in hard disk drives, were used to demonstrate the identification of molecular recognition in tandem with biologically usable magnetic marks. Real-world bio-applications are also being studied, allowing for tailor-made product architecture based on sensor and mark functionality. This detection platform offers a reliable, affordable sensing technique with high sensitivity and substantial scope for quantitative signal results, allowing magneto resistive biochips to address unique diagnostic needs that are not fulfilled by current technologies.*

***KEYWORDS:** chemo selectivity, immobilization, protein biochips, protein patterns, regioselectivity.*

INTRODUCTION

Sensors that track properties such as temperature, friction, strain, or flow offer a closely connected feedback signal to the target parameter. On the other hand, magnetic sensors differ from most of these detectors, since they do not very often directly measure the physical property of interest. They sense shifts, or fluctuations in magnetic fields produced or changed by artifacts or events. Therefore, magnetic fields can carry information about properties such as direction, presence, rotation, angle, or electrical currents which are converted by the magnetic sensor into an electrical voltage. Magnetic fields are absolutely measured by the small amount of magnetic sensors, like earth fields in compassing.

For translation into the desired parameter the output signal requires some signal processing. Obviously a propagation of a magnetic field depends on distance and the form of the producing or disrupting force (i.e., magnet, current, etc.) or occurrence. Therefore it is always important to consider both sensor and object creation in the design of the application. Although magnetic sensors are somewhat harder to use, they do provide accurate and reliable data — with no physical contact. The idea of the protein microarray or protein biochip has arrived at an enticing method for fast sampling of entire proteomes. Hundreds of proteins can be found on a chip using techniques developed for the development of DNA microarrays. A biological sample may subsequently be scattered on the chip, and binding proteins can be identified. Through methods such as fluorescence imaging, time-of-flight mass spectrometry, and peptide mass fingerprinting, the protein of interest will then be analyzed[1].

A microarray of DNA (also commonly called a DNA chip or biochip) is a collection of microscopic spots of DNA attached to a solid surface. Scientists use DNA[2] microarrays to simultaneously measure the expression levels of large numbers of genes, or to genotype multiple regions of a genome. Each DNA spot contains Pico moles (10−12 moles) of a specific DNA sequence, known as probes (or reporters or oligoes). These can be a short section of a gene or other DNA element that are used to hybridize a cDNA or cRNA (also called anti-sense RNA) sample (called target) under high-stringency conditions. Sample-target hybridization is typically detected and quantified by detecting targets

labelled with fluorophores, platinum, or chemiluminescence to determine the relative abundance of nucleic acid sequences within the target. The original nucleic acid arrays were about 9 cm / 12 cm macro arrays and the first computerized image-based analysis was published in 1981[3].

These protein biochips promise a fast , high-throughput means of profiling disease-related proteins or testing protein – protein and protein – drug interactions, which was previously only possible using methods such as western blotting and immunosorbent enzyme-linked assays (ELISA). Despite this concept's promise and potential, protein chips, with a few exceptions, have been only sparsely incorporated into drug discovery science. Although the benefits of these protein micro-arrays give parallel DNA microarray technology, especially with regard to the necessity of only small amounts of useful and costly samples and reagents, the comparison with DNA arrays is more obvious than true. Creating protein arrays requires more steps and is more complicated than building DNA microarrays, particularly due to the reactive nature of proteins, which often contributes to (partial) denature after chemical treatment and immobilization.

The additional driving factor for protein biochip production emanates from relevant biotechnological areas, such as biosensor creation and implementation, biocatalysts, and bio analytics. There has been a recent change in these fields towards producing surfaces that show proteins in tightly regulated patterns, preferably with precision on a nanometer-scale. The continuing miniaturization of bio devices and biomaterials is important to tackle fundamental and functional concerns relevant to dynamic interfaces, such as those faced between biological organisms and artificial systems and computers. One of the primary challenges of manufacturing a successful protein chip is the proper selection of a solid surface and the production of surface chemistry that is consistent with a variety of proteins while preserving their consistency, natural conformation and biological function. Furthermore, chemical selectivity should be regulated by the protein attachment on the chip[4].

Verify which functional groups or protein tags are involved in the Immobilization. In addition, regulation of region selectivity is important, that is, when either one or more protein orientations are preferentially adopted on the surface. Therefore, schemes for one-stage processing should be implemented whenever feasible, as opposed to procedures involving a second step or more comprehensive protein modifications before immobilization[5].

Usually, protein chips are prepared by immobilizing proteins on chemically activated glass slides using a touch spotter or a noncontact microarray, all of which are easily accessible in the high-throughput fabrication of DNA microarrays. Nonetheless, the desire to not only fabricate clusters of protein spots but to create patterns on a surface or to attain feature sizes in the nanometer regime has driven the development of numerous structuring methods that are commonly utilized in nanotechnology and materials science. For eg, dip-pen nanolithography (DPN) [6]gives access to the smallest features, and makes for a smaller chip size and far more sensitive sites than traditional microscale robot spotting techniques.

Another significant barrier to the effective use of protein biochips is the development of appropriate detection strategies. A wide range of techniques have been developed, such as fluorescence imaging, surface Plasmon resonance (SPR)[7], and methods based on mass-spectrometry. In a variety of outstanding analysis papers, certain approaches are de-scribed. The aim of this analysis is to put together chemical, biological, and nanotechnology strategies for protein biochip production. Therefore this study, addressing the following research questions: 1) what are the different type of material which can be used in biosensor chips? And 2) what is a bio sensor and how it works?

LITERATURE REVIEW

This paper relates to a lightweight biosensor framework with giant magneto-resistive (GMR) sensors that are ideal for the identification of superparamagnetic nanoparticle marks. The platform consists of

disposable biosensor cartridges and an electronic reader which allows for high analytical output quantitative detection combined with robustness, ease of use and low cost. Magnetic labels are excited at high frequency, in order to optimize the signal-to - noise ratio (SNR). Wires, which are integrated into the sensor chip's silicone, are used to generate a well-defined magnetic field on the sensor surface, thus eliminating the need for mechanical alignment with external devices. To achieve optimum detection accuracy a signal modulation scheme is applied. The platform is scalable and can be adapted to the specific demands of the application. Experimental findings indicate that three beads with a diameter of 300 nm can be detected on a sensor surface of 1500 μm2 for a measuring time of 1 s[8].

Basis of magneto resistive bio sensing

A biosensor may be specified as a 'compact analytical system or unit integrating an incorporated or related sensitive biological or biologically derived part with a physio-chemical transducer. Since a revival in interest in such instruments in the 1990s, the area in biosensor science is now vast, one of the leading factors being the ongoing growth of microfabrication technologies. Previously, magnetic field sensors such as superconductive quantum interference devices (SQUIDS) and induction coils were used in bio diagnostics but their use was constrained by large scale, poor sensitivity and high power consumption. The use of magneto resistive (MR) materials has surmounted this. A difference in a material's resistivity because of a magnetic field is called a magneto resistive effect. Thomson first recorded this in 1856, but it was not until the late twentieth century that developments in solid state technology, such as the manufacturing of extremely thin and soft MR ferromagnetic films (Ni80Fe20), allowed the widespread techno-logical implementation of the concepts involved.

In the 1980s, the discovery of antiferromagnetic interlayer exchange coupling and the giant magneto resistive (GMR)[9] effect opened up many uses for high-sensitivity magnetic nanostructures, including magnetic storage tubes, read heads and MRAM.

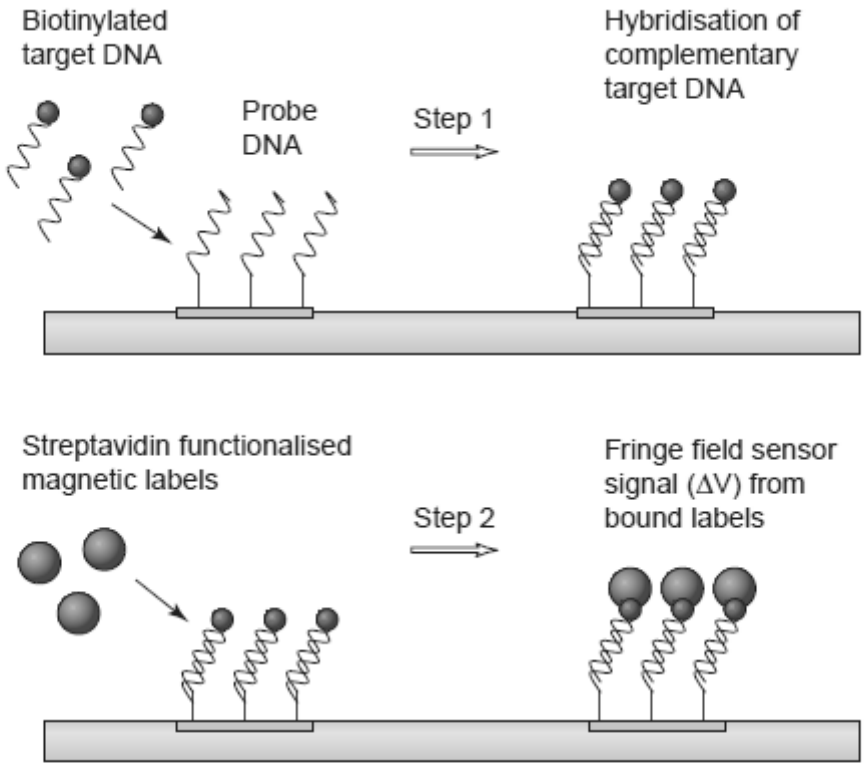

Figure 1. Simplified cross-sectional scheme for the use of magnetically labeled streptavidin to detect the location of pre-hybridized biotinylated DNA on-chip. A post-hybridization magneto resistive DNA chip detection strategy. Step 1: probe DNA immobilized over on-chip magneto resistive sensors are hybridized with biotinylated target DNA. Step 2: magnetically labeled streptavidin is used to detect the hybridized DNA by binding to the biotinylated hybridized target DNA. The magnetic fringe field of the labels is detected by the sensors.

The anisotropic magneto resistive effect (AMR) is the product of the change in material resistance which occurs when the magnetization changes from parallel to transverse with respect to current flow direction. This influence is found in ferromagnetic alloys and is the basis for single thin-film sensors, such as the planar Hall sensor and the AMR ring sensor. The GMR effect is based on the spin-related interfacial and bulk-scattering asymmetry observed for spin-up and spin-down conduction electrons crossing ferromagnetic – nonmagnetic – ferromagnetic multilayer structures where the parallel or antiparallel alignment of the ferromagnetic layers can be formed. The relative orientation of the magnetizations of the two magnetic materials is modified by an applied magnetic field. When combined, the structure's electro-resistance is weak. The resistance is high when the magnetizations are arranged in antiparallel fashion. It is the basis of both GMR sensors and spin valves, which are used as read heads in most computers to calculate the fringe magnetic field generated by magnetized regions on the track (bits).

Reactive Polymer Surface Interfaces

Materials which help polymer are potentially useful alternatives to surfaces which are inorganic. The inexpensive processing of polymers makes its use especially appealing in commercial applications. For example, the most widely used microtiter plate material in ELISA applications is polystyrene, and a wide range of micro fabricated devices are also based on polymers. Such polymeric systems are

increasingly being available for installation in existing standard micro array equipment. Large cases of such devices are microfluidic chips, which are usually manufactured from polymeric materials such as poly (dimethyl siloxane) (PDMS), poly(methyl methacrylate) (PMMA), and polycarbonate (PC). Chemical surface modification of these polymers is needed for protein immobilization, as they lack sufficient functional groups in their native form. For example, PDMS can be treated with plasma oxidation, which allows PMMA to be treated with 1,6 hexane diamine to functionalize with organosilanes to obtain an aminated surface that is suitable for subsequent protein immobilization. Sulfonating of the surface with sulfate groups was described in the case of a PC.

Detecting magnetic labels

The labels used are paramagnetic beads which are non-remain. Inside the mark the magnetic substance occurs as small particles (usually iron oxide), with occasional random moments. The detection method depends on the synchronization within the mark of these moments to create a measure-able fringe area. Therefore, a magnetic field is applied to the device using an electromagnet coil or horseshoe. The electromagnet is used to cause an average moment in the labels and also to focus the sensors; that is, to distort the sensors in their magneto resistive reaction curve (MR curve) within the linear system. The orientation of the applied field, which is either perpendicular to the chip surface or parallel to the surface (in-plane) for present sensor geometries and at a right angle to the sensor length], depends on the sensor used, although certain sensors, such as spin valves, can be used in either way. Figures 1a and b, respectively, represent the measuring schemes for a spin valve or Hall cross sensor.

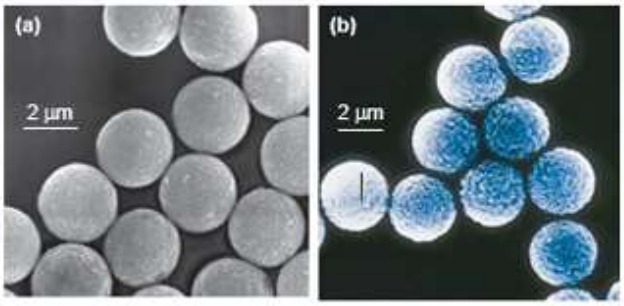

Figure 2. SEM images of magnetic microspheres. Scanning Electron Microscope (SEM) images of magnetic microspheres showing uniform size and shape: (a) 3 mm Micromerw-M, image courtesy of Micromod and (b) 2.8 mm M280 Dynabeads, image courtesy of Dynal Biotech.

Magnetic labels

Magnetic labels or containers, also known as micro cones, microbeads and nanoparticles, have seen wide-ranging scientific and therapeutic uses in biotechnological and biomedical science, most especially in the fields of bio separations, molecular biology and drug distribution. The most important characteristics of magnetic labels used in biosensors or biochip systems are size and form, chemical and magnetic com- position, surface properties, stability and ease of chemical processing for the immobilization of biomolecules. The biochemical functionalization of the magnetic label used depends on the device's intended application; the label’s size and magnetization depends on the size and strength of the sensors included, and the need to avoid blockage or fouling of the device's microfluidic components during study. The size of the mark used can range from a few microns in diameter to a few nanometers, so scale will be used as a basic labeling tool here.

Magnetic microspheres

The bigger labels (1–3 mm diameter) were the most commonly tested using various types of MR sensors in early detection experiments. Use non-specialized light microscopy methods, they are readily detected and hence enumerable. Use preparative methodologies such as cone-filling or core-shell methods, they may also be generated in a uniform size and shape. In fact, despite having a lower magnetic compound section level (.15 percent) compared to magnetic nanoparticles, their decreased volume results in a higher magnetic moment per label in an applied magnetic field, allowing for distinct single-label detection signals.

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Magnetic nanoparticles

Smaller nanometer-sized labels with a high magnetic (iron-oxide) content (70 – 85 per cent) offer a solution to these problems; the smaller scale allows improved label binding density around the sensor surface. Unfortunately, most commonly accessible magnetic nanoparticle substance samples presently produce particles of heterogeneous size (e.g. 200 – 400 nm) and form (non-spherical) and thus hinder quantification. In addition, their high resultant magnetization and anisotropy for their volume in an applied magnetic field can contribute to rapid clustering (single particles aggregating to form groups). Permanent clustering of labels, which can not be remedied with a discriminatory magnetic force applied to the chip or on-chip washing cycles, can result in exaggerated positive signals because non-biologically bound labels may remain attached to biologically bound labels. Finally, given the higher magnetic percentage structure, magnetic nanoparticles as detectable marks gain a lower magnetic moment in an equal applied field than a magnetic microsphere. Lesser labels thus require increasingly more sensitive sensors and measurement devices. Many of the labels used to date is based on iron oxide (magnetite or magnetite), while transition metal forming nanoparticles (e.g., NiFe or CoFe) providing higher magnetization is currently being examined.

MOVING AHEAD IN MAGNETO RESISTIVE BIO SENSING

Magneto resistive instruments such as large GMR sensors and spin valves have been used as a basis for the development of biochips to detect a range of commercially usable magnetic microbeads and magnetic Nano particles. The identification of molecular recognition (the association of complementary or affinity-linked biomolecules) was demonstrated using two forms of streptavidin functional magnetic labels (micrometer and nanometer size) and sensor-linked biotin and biotin-streptavidin binding pair as a way of detecting on-chip hybridized DNA. Recent advances involve ongoing improvements in system architecture and examples of these technologies' effectiveness in real-world biological applications. The styles of MR sensors currently under review include large GMR sensors and spin buttons, magneto resistive anisotropic ring (AMR) sensors, and hall crosses. Promising prospects for future research include planar Hall Effect sensors and junctions to magnetic tunnels. Many magnetic field sensors used in bio diagnostic instruments include SQUIDS and inductive coils.

Magneto resistive detection signals

The MR sensors used to detect magnetic labels vary in scale, shape, composition, and performance, resulting in varying sensitivity ranges, dynamic range, and signal: noise ratios to detect the same scale and magnetization magnetic label. An initial attempt was made to compare and contrast the different

types of sensor used, though this was hampered by the various developmental measurement systems used under different experimental conditions. The sensor signal received (voltage change) depends on the sensor's intrinsic magnetic susceptibility and other physical parameters such as the label: sensor size ratio, the label 's magnetic moment, the distance between the label and the sensing substrate, the sensor current, and whether or not signal amplification techniques are being used. The moment of the mark is related to the applied magnetic field, which depends on the magnetic structure and material. The moment increases with an increase in applied field, with a linear response, until the field becomes saturating and the moment no longer increases. Sensor signals recorded for single micron magnetic labels differ according to the sensor and the device set-up (Table 1). Sensitivity of the system and its dynamic range can be represented either magnetically or biologically. The magnetic susceptibility may be considered as the lowest observable magnetic moment or as the smallest magnetic mark of a specific magnetic composition. Biologically speaking, sensitivity can be considered as the smallest amount of observable biomolecular interactions, or the lowest concentration of target biomolecule needed to generate a binding signal. The dynamic range can also be represented in both directions, but is represented more clearly as the spectrum of the amount of labels that a single sensor can sense, or the spectrum of target biomolecule concentration tractions that can be quantitatively defined by a single sensor. Briefly, it appears to date that small spin valves provide the best sensitivity with reasonable signal: noise ratios, large GMR sensors provide improved dynamic range, planar Hall sensors provide ease of manufacturing and AMR rings have the perfect configuration for single microsphere detection.

Table 1: Magneto resistive sensors and magnetic labels used to date in magneto resistive detection platforms.

Sensor Type	Size (mm)	Label size	Sensitivity	Range	Molecular Recognition?
Spin valve	3 £ 7	1.99 mm	1	1 – 6	Yes
		0.5 – 1.5 mm		1 – 10	No
		0.9 mm		1 – 15	No
		249 nm	10 s	10 – 100 s	Yes
		99 nm	100 s	1000 s	No
		49 nm	1000 s	1000 s	No
Spin valve	2 £ 2.49 – 2.99 £ 12	2.9 mm	1	~ 10	No
		10 nm (Co)	~ 1000 s	–	No
AMR ring	5 (d)	4.5 mm (NiFe)	1	–	No
Hall sensor	2.5 £ 2.5	2.9 mm	1	–	No
GMR spiral	70 (d)	2.8 mm	200	~ 1000	Yes
GMR strip	4.99£ 79	2.8 mm	1	~ 100	Yes
GMR serpentine	199 (d)	2.8 mm	10	~ 1000	Yes

Magneto resistive biochips

The biochip consists of an arrangement in a sequence of sensing zones with single or multiple bio sensing elements engineered and assembled on-chip to allow multi-sample or multi-analyte-based detection. The first aspect of chip design is the layout. The chip measurements (usually mm scale) are specified and the available chip surface is used as effectively as possible to optimize the active sensing region for each sensing field, integrate correct reference sensors, while preventing electrical, magnetic or thermal cross talks between sensors or structures on the device.

In a Wheatstone bridge structure, a differential sensor set-up uses a reference sensor to allow thermal and electrical (mains) drift correction between a biologically active sensor and a biologically inactive sensor. Figure 5 demonstrates the configuration of a first-generation biochip, based on spin valve sensors. This chip was made from 12 pairs of sensors, used for single and differential applications

Measurements by instruments. Such structures were assembled using microelectronic processing techniques under cleanroom conditions on 30 silicon wafers. The structures are defined using laser

lithography, and sputtering deposition of sensor materials. During chemical and biological reactions a protective (passivation) coating was placed over the chip surfaces to prevent degradation of the chip surface by fluids added. This coating (substrate) should also promote surface mobility for the immobilization of biomolecules and should preferably demonstrate low non-specific adherence to magnetic markers, polymers, proteins, and nucleic acids. In conjunction with aqueous phase biochemistry, sputtered silicon dioxide was used without problems. Just the electrical contacts at the chip's outer edges remain free from passivation material.

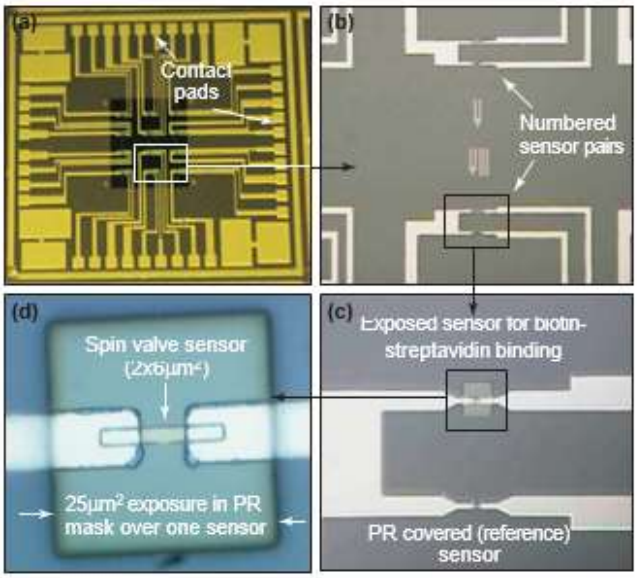

Figure 3. A magnetoresistive-based biochip designed with 12 pairs of spin valve sensors, used for single or differential signal measurements. (a) The 8 £ 8 mm chip has the sensor pairs fabricated in the central area, covered with photoresist (PR) mask, the sensor connections running to contact pads arranged around the outer edges of the chip. (b) Each sensor pair has one input line and two separate output lines. (c) One sensor of each pair is exposed to on-chip biochemistry (active sensor) via an exposure in the photoresist. (d) A single 2 £ 6 mm2 spin valve with contacts within a 25 £ 25 mm2 exposure in the PR mask.

The wafer is divided into individual chips, and each is mounted in a chip carrier for easy hardware connection. The connections are wire-bonded to the plates, and are then secured by a silicone coating, or microfluidics are used to regulate fluid movement through the chip. As described in the references in Table 1 the microelectronic manufacturing techniques for other sensors and chips may vary.

Reactive Interfaces on Silicon

Besides glass, silicone has also been used as a surface material for biochip manufacturing. In the semiconductor industry, silicon wafers are used on a large scale because these chips have high electrical conductivity, high solvent resistance, good mechanical stability, and low intrinsic fluorescent cence. However, the chemical functionalization of silicon surfaces is complicated by the fact that silicon oxidizes naturally in the soil to create an amorphous film of silica.

Thus, surface modification strategies for the formation of covalent silicon – carbon bonds need, first, special silicon surface pretreatment to eliminate the oxide layer and, second, silicon surface activation for subsequent reaction with organic molecules (Scheme 3). This activation is usually accomplished by treating the silicon surface with HF to produce a hydrogen-terminated Si(111) surface that can react more to ultraviolet irradiation or thermal activation with unsaturated w-functionalized alkenes. Instead,

if silicon becomes oxidized with plasma (ionized gas), an equivalent feature to glass slides may be achieved with organosilanes.

In recent years, different techniques have been developed to functionalize a number of alternative oxide surfaces that are of specific importance for advanced applications such as implants (titanium, tantalum, and niobium), electrical instruments (indium tin oxide (ITO) and diamond), and others, such as silicate minerals (mica). Silane chemistry and electro polymerization procedures were applied in the case of ITO, while photo immobilization was used to activate diamond. In addition to silane chemicals, (poly)electrolytes were used to functionalize mica, while monolayer (SAM) formation using thiols and phosphonates was also reported for titanium, tantalum and niobium self-assembled.

CHIPS WITH 3D MATRIXES

Instead of spotting proteins onto a solid surface of two dimensions, molecules can diffuse into a porous matrix created by polymer membranes or hydrogels. Such matrixes display high protein immobilization potential and can provide a more homogeneous "normal" aqueous environment than flat surfaces, thus preventing protein denaturation. It suffer, though, from issues relating to the influence of mass transit and also from strong noise signals. Traditional membrane materials used are nitrocellulose and nylon, the latter offering greater physicality

Power and ability to bind. Nylon adhesion to proteins is therefore usually more stable than nitrocellulose. Nylon makes positive or negative electrostatic interactions or photo-cross-linking, although it is suspected that nitrocellulose binds proteins by hydrophobic interactions. Casting these membranes onto the glass surface improves their stability and thus improves spot resolution from 0.5–1 mm to 25–200 mm, allowing them to be applied in microarray technology. Anodically oxidized porous alumina provides further enhancement of the mechanical stability. Such substance provides readily available surface chemistries, in particular methods of salinization, which can lead to higher densities of biomolecular samples and thus greater sensitivity in applications for arrays.

Polymeric hydrogels reflect hydrophilic matrixes into which proteins can migrate, resulting in an immobilization efficiency that is up to 100 times greater than that found in planar surfaces. Covalent bonding of the gels to solid surfaces allows secure microarray chips to be produced. Agarose and acrylamide, for example, can be photo polymerized to a functionalized surface with acrylic groups. The polymer can subsequently be activated using hydrazine or ethylene diamine to produce amine groups on the surface. Certain polymeric gel surfaces that can be used for protein immobilization contain polysaccharides, such as chitosan or dextran.

Chitosan is an amine-modified, edible polysaccharide that is non-toxic, so it is biodegradable. It can be simultaneously immobilized on glass supports due to its pH-responsive properties, and bind proteins by electrostatic interactions. Dextran is a complex branched polysaccharide consisting of glucose molecules that are joined into chains of varying length. Dextran hydroxyl groups can be oxidized to stable aldehyde ties and can then be covalently immobilized on amine-based supports.

This mixture shapes the surface of Biacore commercial plates. Unreacted groups of aldehyde may also be used for immobilization of proteins. Figure 3 demonstrates the use of lysine-functionalized poly (ethylene) glycol (PEG) that was found on aldehyde-coated glass slides; immunoglobin G (IgG) was subsequently immobilized. Recently, super molecular hydrogels consisting of glycosylated amino acids have been developed as protein array surface material. Biodegradable polyesters such as poly (L-lactic acid) and its numerous copolymers containing D-lactic acid and glycolic acid were also studied as biological surfaces.

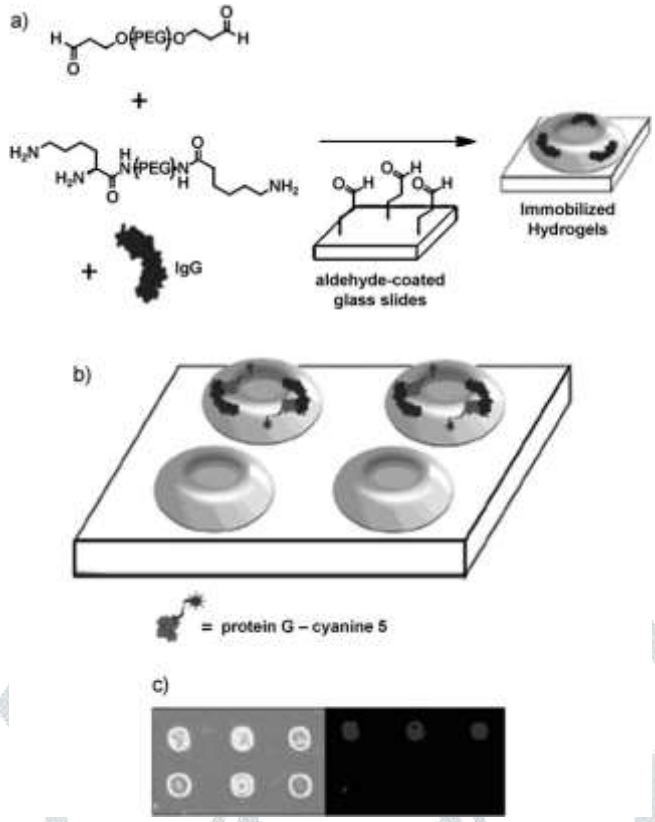

Figure 4. a) Hydrogels created from aldehyde- and lysine-functionalized poly (ethylene glycol) (PEG) and containing IgG were spotted onto aldehyde-coated glass slides to create gel pockets attached to the glass slides. b) Incubation of the IgG-containing hydrogel spot array with Cy5-labeled protein G allowed detection of IgG-containing hydro- gel spots. c) Optical (left) and fluorescence images (right) of the hydrogel spots. Spot diameter is approximately 200 mm. Only the top row of hydrogel spots, which contain IgG, show fluorescence. Reproduced with permission from ACS.

Biological considerations

The MR sensing technique is versatile in that it can potentially be used to detect and analyze nucleic acids, proteins, whole cells or microorganisms that are magnetically labeled. The most obvious areas of immediate application are perhaps the DNA chips and protein chips for immunoassay. The choice of developed DNA chip depends largely on the nature of the received sensor signals. Profiling the gene expression (measuring a difference in gene expression) requires a chip devoted to the analysis of upregulated or downregulated genes in a sample with a control gene.

It includes purely quantitative analysis, i.e., discernible and reproducible variations in the sensor signals collected on the chip at different DNA probe sites. Sensor systems with a larger dynamic size (the size of the number of magnetic labels per signal detected) should be preferred in this scenario. DNA chips for the detection of DNA mutation sites [most importantly, the detection of single nucleotide polymorphisms (SNPs)] may require only qualitative ('yes or no') signals, but they require the ability to discern between very small differences in the two-strand sequence. Such a chip will ideally have multiple sensing zones; the numbers of SNP's or other mutations associated with certain diseases are always very high. So a lot of probes are expected. It presents a greater technological obstacle in the production of MR chips, since effective multiplexing involves a significant number of sensors per device. Specific issues to overcome include preparing actual samples (cell / tissue) prior to the detection phase. That requires careful consideration of the appropriate methodology for labeling and the correct approach to be used in detection.

Several researchers used the biotin – streptavidin binding model to show the simple proof of concept of the MR chip, using different MR sensors. This model was chosen because streptavidin has four biotin binding sites and the two exhibit very high binding affinity and high binding strength; biotin can also be used as a biochemical label for nucleic acids and proteins, allowing the use of streptavidin functionalized magnetic labels to detect biotinylated target molecules as discussed. This method may also help inhibit the biological association of magnetically labelled target molecules with a sensor-bound molecule from steric interference.

There has been evidence of post-hybridization identification of DNA on MR chips, but that often involves a time-consuming traditional on-chip hybridization stage. More recently, in conjunction with spin valve sensors, we have used magnetic field producing current lines for the rapid and simultaneous identification of on-chip hybridization using magnetically labelled target DNA. This is achieved by using the magnetic fields generated by tapered current lines to quickly focus, at sensor sites, on magnetically labeled target DNA. In this case, hybridization and detection of DNA can take place in minutes using an MR biochip, using very low target DNA concentrations

Protein chips pose particular problems, often related to the complex secondary and tertiary protein structure, resulting in a higher degree of precision needed for effective recognition. Despite this, we believe that MR biochips have strong potential applications in micro-assays based on high sensitivity proteins and anticipate publication in this area in the near future.

PROTOTYPE DEVICES AND SPECIFIC APPLICATIONS USED

High GMR sensors and a bead-capture technique were used by two versions of concept bead array counters (BARC, II and III). The BARC III chip uses a 64-sensor element array arrangement outlined in Figure 6a, designed to allow for quantitative linking signals with regard to the percentage mark coverage. These devices, which are the most advanced in a final system to date, have been adapted to the application of DNA chips; more importantly, to the identification of biological warfare agents such as Bacillus anthracis, Yersinia pestis, Brucella suis, Francisella tularensis, Vibrio cholerae, Clostridium botulium, Campylobacter jejuni and Vaccinia viruses. This mixture shapes the surface of Biacore commercial plates. Unreacted groups of aldehyde may also be used for immobilization of proteins. Figure 2 demonstrates the use of lysine-functionalized poly (ethylene) glycol (PEG) that was found on aldehyde-coated glass slides; immunoglobin G (IgG) was subsequently immobilized. Recently, super molecular hydrogels consisting of glycosylated amino acids have been developed as protein array surface material. Biodegradable polyesters such as poly (L-lactic acid) and its numerous copolymers containing D-lactic acid and glycolic acid were also studied as biological surfaces.

CONCLUSION

Detection of single micron-sized magnetic labels based on MR has been explicitly shown and supported by theoretical magnetic simulations. Detection of single magnetic nanoparticles (.100 nm) is expected in the near future, paving the way for easier applications for single-molecule detections. The MR approach provides a stable labeling system with low-cost components in terms of DNA chips in what will ultimately provide compact, user-friendly detection devices. At this point in their growth, MR biochips in terms of the amount of on-chip / on-slide DNA probe elements do not interact with DNA microarray.

In addition to low cost, the most immediate benefit of MR biochips can be in tandem with magnetic field-generating chip architectures that can be used to easily target magnetically labelled biomolecules at sensor sites, thus greatly reducing hybridization time or other molecular recognition processes. Nanogen has already commercialized the use of electric fields for this purpose, but this biochip technology still employs costly fluorescence-based detection. For a variety of biological applications,

MR biochips currently reflect a young yet rapidly growing research field, offering high sensitivity, high-quality quantitative molecular detection results.

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